# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.**

# PATENT SPECIFICATION

(11) 1 467 560

1 467 560

(21) Application No. 48709/75 (22) Filed 27 Nov. 1975
(44) Complete Specification published 16 March 1977
(51) INT CL² C07D 317/58
(52) Index at acceptance
C2C 1494 213 246 247 253 25Y 30Y 313 31Y 321 32Y 332 339 360 362 36Y 453 45Y 619 620 621 623 650 651 652 708 MJ NM

(72) Inventor JOHN T. SUH

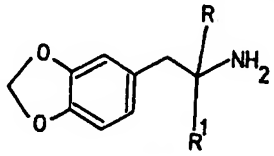
(19)


## (54) PREPARATION OF ETHYLAMINE DERIVATIVES

(71) We, NICHOLAS INTERNATIONAL LIMITED, a Company organised and existing under the Laws of the State of Victoria, Commonwealth of Austrailia, of 33 Albert Road, Melbourne, Victoria, Austrialia 3004, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

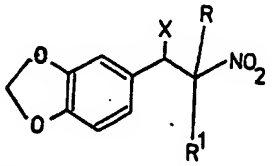
The present invention relates to a process for preparing ethylamine derivatives.

The invention provides a process for preparing compounds of formula I




I

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl) which comprises catalytically hydrogenating a compound of formula IV

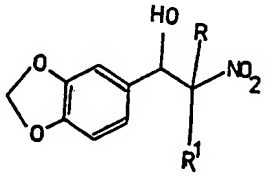



IV

(wherein R and $R^1$ are as defined above and X is halogen) using platinum oxide as catalyst.

The hydrogenation step of the above process is preferably carried out at super-atmospheric pressures and at elevated temperatures typically at pressures of about 1000 p.s.i. and at about 100°C. The yield in the hydrogenation step is usually in the range 63—95% when platinum oxide is used as catalyst and both dehalogenation and reduction of the compound of formula (IV) can be achieved in a single step whereas other catalysts based, for example, on palladium or nickel have been found to give unsatisfactory yields (20—35%) and to give products which are heavily contaminated with various undesirable by-products.

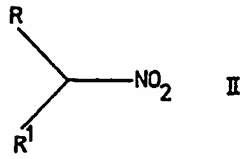
The compounds of formula IV can be prepared by halogenating a compound of formula III




III

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl).

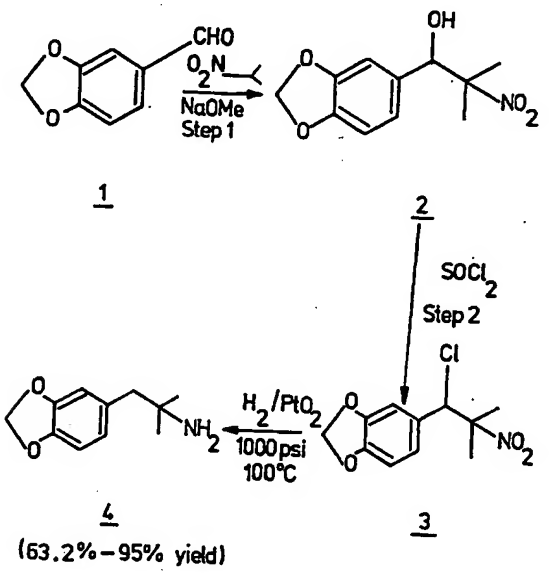
The compounds of formula III can be prepared by treating piperonal or a functional derivative thereof with a compound of the formula II



II

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl).

The preparation of the compound, 1,1-dimethyl-2-(3,4-methylenedioxyphenyl)ethylamine is illustrated in the following reaction scheme:




(63.2%–95% yield)

The compounds produced according to the invention are useful as intermediates in the preparation of the pharmaceutically useful (bronchodilator) compounds described and claimed in United States Patent Nos. 3 700 692 and 3 786 154 and UK Patent No. 1 358 005.

The invention is illustrated in the following Example:

## EXAMPLE.

Preparation of 1,1-Dimethyl-2-(3,4-methylenedioxyphenyl)ethylamine

(a) *1,1-Dimethyl-2-hydroxy-2-(3,4-methylenedioxyphenyl)nitroethane*

A solution of 55.2g (2.4g atom) of sodium in 2.62 litres of methanol cooled to 25°C was added to 684g (689.5ml; 7.68 moles) of 2-nitropropane after which 360.4g (2.4 moles) of piperonal were added. The solution was stirred at room temperature for 18 hours, cooled in an ice bath and acidified with 2.4 litres of 1N sulphuric acid. The resulting mixture was diluted with 5 litres of water, and an oil which precipitated was syphoned off and added to a rapidly stirred solution of 187.4g (1.8 moles) of sodium bisulphate in 1.2 litres of water. The mixture was stirred for 15 minutes, after which the solid which formed was separated and washed three times with ether. The organic layer was separated off, washed with brine, dried and concentrated to an oil which was crystallised from a mixture of 250ml of toluene and 850ml of hexane to give 1,1-dimethyl-2-hydroxy-2-(3,4-methylenedioxyphenyl)nitroethane m.p. 88—91° (Yield 200.4g). The mother liquor from the crystallisation was diluted with a further litre of hexane to give a further crop of the product, m.p. 88—91° (49.9g; total yield 250.3g, 43.6%).

(b) *1,1-Dimethyl-2-chloro-2-(3,4-methylenedioxyphenyl)nitroethane*

A solution of 242.8g (1.016 moles) of 1,1-dimethyl-2-hydroxy-2-(3,4-methylenedioxyphenyl)nitroethane in 500ml of benzene was treated with 139g (84ml, 1.17 moles) of thionyl chloride, after which the mixture was refluxed for 4 hours, cooled slightly and concentrated to a dark yellow oil which crystallised on cooling and seeding. The resulting solid was broken up and dispersed in 150ml of 2 - propanol after which it was separated, washed twice with cold 2 - propanol and dried to give crude 1,1 - dimethyl-2-chloro-2-(3,4-methylenedioxyphenyl)nitroethane as a light yellow solid m.p. 63—66°C (yield 230.9g). A 201.3g portion of the crude product was treated with "Darco" (Trade Mark) activated carbon and recrystallised from 402ml of SDA—30 to give 181.6g (79.6%) of the pure product as a white solid m.p. 65—67°C).

(c) *1,1-Dimethyl-2-(3,4-methylenedioxyphenyl)ethylamine*

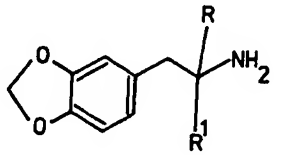
A mixture of 51.52g (0.2 mole) of 1,1-dimethyl-2-chloro-2-(3,4-methylenedioxyphenyl)nitroethane, 2.0g of 83.8 weight % purity platinum oxide, 13.0g (0.22 mole) of sodium acetate and 4.0g of "Darco" in 96ml of acetic acid and 500ml of SDA—30 was stirred under a hydrogen atmosphere at 1000 p.s.i. and 100°C for a period of 5 hours, after which uptake of hydrogen ceased. The solution was cooled and filtered, and the filtrate was concentrated to an oil which was treated with 400ml of water. The mixture was extracted twice with ether, after which the aqueous layer was made alkaline by addition of 20% aqueous sodium hydroxide and extracted four times with chloroform. The combined extracts were filtered through "Dicalite (Trade Mark) diatomaceous earth product, washed with water, dried and concentrated to a light yellow oil which was distilled using a 2 inch 19/30 joint size distillation column to give 1,1-dimethyl-2-(3,4-methylenedioxyphenyl)ethlyamine as a clear colourless oil, b.p. 68—85°C. 0.6—0.04 mm Hg (Yield 24.4g, 63.2%).

*ANALYSIS*

Calculated for $C_{11}H_{15}NO_2$: C, 68.37%; H, 7.82%; N, 7.25%.
Found: C, 68.15%; H, 7.16%; N, 7.16%.

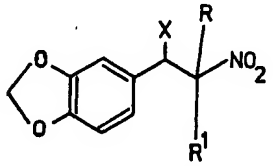
WHAT WE CLAIM IS:—

1. A process for preparing a compound of formula I



I

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl) which comprises catalytically hydrogenating a compound of formula IV



IV

(wherein R and $R^1$ are as defined above and X is halogen) using platinum oxide as catalyst.

2. A process as claimed in Claim 1 wherein said hydrogenation is carried out at a pressure of about 1000 psi and at a temperature of about 100°C.

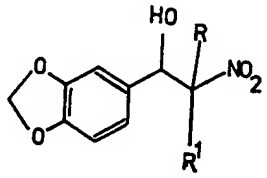
3. A process as claimed in Claim 1 or Claim 2 wherein R and $R^1$ are both methyl.

4. A process as claimed in any one of Claims 1 to 3 wherein X is chlorine.

5. A process as claimed in Claim 1 and substantially as hereinbefore described in section c of the Example.

6. A compound of formula I whenever prepared by a process as claimed in any one of the preceding Claims.

7. A process as claimed in any one of Claims 1 to 5 wherein the compound of formula IV is prepared by halogenating a compound of formula III



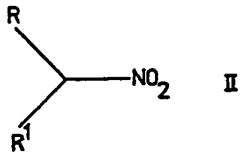
III

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl).

8. A process as claimed in Claim 7 and substantially as hereinbefore described in sections b and c of the Example.

9. A compound of formula I whenever prepared by a process as claimed in Claim 7 or Claim 8.

10. A process as claimed in Claim 7 or Claim 8 wherein the compound of formula III is prepared by treating piperonal or a functional derivative thereof with a compound of the formula II



II

(wherein R and $R^1$ independently represent hydrogen or $C_1$—$C_4$ alkyl).

11. A process as claimed in Claim 10 and substantially as hereinbefore described in the Example.

12. A compound of formula I whenever prepared by a process as claimed in Claim 10 or Claim 11.

W. H. BECK, GREENER & CO.,
7 Stone Buildings,
Lincoln's Inn,
London WC2A 3SZ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.